

Increased Risk of Birth Defects and Developmental Disabilities in Children Born Through Assisted Reproductive Technologies

Children whose conceptions were aided by infertility treatments such as the **assisted reproductive technologies (ARTs)** are at increased risk of **fetal growth restriction, birth defects, and developmental disabilities** in comparison to children whose conception were unassisted by such treatments.

General Information

Broad Focus Area	Exposures to Chemical Agents
<p>Background and Justification</p>	<p>ARTs are defined as those infertility treatments in which both oocytes and sperm are handled in the laboratory; these include in vitro fertilization-transcervical embryo transfer, gamete and zygote intrafallopian transfer (gametes or zygotes transferred into fallopian tubes rather than uterus), frozen embryo transfer, and donor embryo transfer. ART is recognized as an important contributor to the U.S. low birth weight rate because of the known association between the use of ARTs and multiple births,¹⁻³ and between multiple births and low birth weight.⁴ Additionally, studies have suggested that low birth weight rates are increased among singleton infants conceived with ARTs as compared with naturally conceived infants or population-based rates.⁵⁻¹³ These previous studies were limited in their assessment of specific treatment-related effects. Moreover, questions remain about whether the reported low birth weight risk for singletons conceived with ARTs is a direct effect of the procedure or reflects some other factor related to the underlying infertility of the couples who conceive using these procedures. A study that closely follows ART patients and their pregnancies prospectively is needed to more definitively address this important question. To date, few studies have specifically evaluated low birth weight due to intrauterine growth restriction separately from low birth weight due to early delivery, and no study has monitored fetal growth changes prospectively.</p> <p>With respect to birth defects, equivocal results exist regarding the association between ARTs and birth defects in the offspring.^{5, 6-9, 11, 12, 14-18} Prior studies have suffered from various methodological problems including low statistical power, particularly to assess individual defects separately, and differential case ascertainment and coding schemes for infants conceived using ARTs and infants conceived naturally. Nearly all studies relied on retrospective registry data. Again, a large, well-designed prospective study is needed to address this question.</p> <p>The study of longer term outcomes such as developmental disabilities among ART children has been hampered by inadequate sample sizes and lost to follow-up. A recent study reported an increased risk for developmental delay and cerebral palsy among children conceived with ART.¹⁹ These effects remained elevated when analyses were limited to singleton births; however, the study suffered from a number of methodological drawbacks including a lack of statistical power to adequately assess subgroup findings. Thus, a large prospective study would greatly advance this important research question.</p>
<p>Prevalence/ Incidence</p>	<p>In the U.S. and worldwide, the use of ARTs to overcome infertility is increasing rapidly. In 1999, the most recent year for which U.S. population-based data are</p>

	<p>available, more than 86,000 ART procedures were performed, resulting in more than 30,000 live-born infants.¹ These infants represent an estimated 0.8% of the total infants born in the U.S. in 1999. This proportion is expected to continue to rise, largely due to improved accessibility and successful treatments. Further, ART treatments represent only a fraction of the infertility treatments currently used. Results from a national survey suggest that, in 1995, treatment with ovulation stimulation medications without ARTs was 30 times more frequent than the use of ARTs, and artificial (or assisted) insemination was 10 times more frequent.²⁰ Thus, the proportion of infants conceived using various infertility treatments is ostensibly orders of magnitude higher than the 0.8% estimated for ARTs alone. In the U.S., the incidence of fetal growth restriction was approximately 5% among the general public.²¹ Birth defects occur in approximately 3% of children born in this country²², while developmental disabilities have been reported in approximately four million Americans.²³ Cerebral palsy affects approximately 0.2% of children²⁴, and autism affects about 0.3%²⁵. The prevalence of cerebral palsy in the United States is increasing, due to the increased survival of very low and low birth weight infants²⁶. Whether the frequency of autism is increasing is controversial, because recent estimates of higher prevalence may be due to inclusion of less severe cases.</p>
Economic Impact	<p>Children with birth defects and/or those born too small contribute disproportionately to infant and pediatric health care costs.^{27,28} A report based on 1988 data estimated an annual incremental increase of \$6 billion in health care, education, and child care costs attributable to children <15 years born low birth weight (LBW), compared to if they had been normal-birthweight.²⁹ While no studies have precisely calculated all of the costs associated with autism, a U.K. report estimates the lifetime custodial costs of autism spectrum disorders in the range of \$3-\$4 million per child, with societal costs likely to be triple the individual estimate.^{30, 31} The lifetime costs of mental retardation for persons born in 2000 were estimated at \$51.2 billion (in 2003 dollars).³² Furthermore, over 25% of pediatric hospital admissions are estimated to occur among children with birth defects.²⁷ Children with developmental disabilities require a host of special education services, medical services, and supportive care. In the U.S., special education costs are estimated at \$36 billion annually.³³</p>

Exposure Measures		Outcome Measures	
Primary/ Maternal	Infertility treatments	Primary/ Maternal	Intrauterine growth
Methods	Questionnaire; Medical record review	Methods	Fetal ultrasound
Life Stage	Prenatal	Life Stage	Prenatal
Primary/Child		Primary/Child	Assessments of birth defects and developmental disabilities
Methods		Methods	- Neurological exams & standard examinations by a medical professional - School record review
Life Stage		Life Stage	Birth through early adulthood

Important Confounders/Covariates

Age	Greater maternal age not associated with higher risk of untoward birth outcomes (1.90% in cases, 1.15% in controls, NS) ³⁴
Parity; previous obstetric outcome	Risk of major birth defects following assisted reproduction is comparable with that of spontaneously conceived pregnancies, matched for age, gravidity, parity, and previous obstetric outcomes. ^{35, 36}

Population of Interest	Estimated Effect that is Detectable
Children whose conceptions were aided by infertility treatments. Over-sampling for participants with ART will be necessary to assess outcomes that occur at prevalences less than 5% of the general population.	Sample size estimates were derived with conservative assumptions of the minimum risk ratio – 1.5 for each of the general outcomes: IUGR, preterm delivery, birth defects, serious developmental disabilities, and mild-serious developmental disabilities; and 2.0 for specific individual or related groups of birth defects or developmental disabilities. Sample sizes vary widely given the range of prevalence rates for the outcome measures. A minimum sample of 4,335 ART pregnancies is needed to study each of the general outcomes with sufficient power to assess ART singletons separately. To study specific birth defects and developmental disabilities, the necessary sample size increases to as much as 8,798 ART pregnancies depending on the prevalence of the defect or disability.

Other Design Issues	
Ethical/Burden Considerations	Couples seeking ARTs are already undergoing intensive and time-consuming medical testing and treatments. It is anticipated that data collection could be structured to coincide with their regular visits to an infertility clinic. Privacy and confidentiality issues are paramount concerns for sampling and data collection procedures.
Cost/Complexity of Data Collection	A sampling strategy that incorporates selected recruitment at infertility treatment centers will be required.

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